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Statistical Thermodynamics Unveils How Ions Influence An Aqueous Diels-Alder Reaction

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Abstract

The kinetics of Diels-Alder (DA) reactions in water has been known to be altered by salts for a long time. Yet the question how salts influence the reaction rate, either as rate-enhancing or rate-reducing additives, has so far remained unresolved. Conflicting hypotheses involve (i) indirect salt contributions through the modulation of internal pressure and (ii) making (or breaking) of the so-called "water-structure" by salts that strengthen (or weaken) the hydrophobic effect. In contrast to the qualitative nature of these hypotheses, here we answer this question quantitatively through a combination of transition state theory and fluctuation adsorption-solvation theory (FAST) using the DA reaction between anthracene-9-carbinol and N-ethylmaleimide as an example. We show that rate enhancement

is driven by the salting out of the hydrophobic reactant, while rate-enhancing salts exhibit stronger affinity to the transition state.

Introduction

Diels-Alder (DA) reactions are considered to be amongst the most important C─C bond forming reactions, offering a practical synthetic procedure in the preparation of cyclic structures.[1,2] Similar to many types of organic reaction,[3] the solvation environment for a DA reaction has a significant impact on its outcome.[4,5] This has been exploited fully in DA-type reactions in aqueous salt solutions, which have the advantage of faster reaction rates in comparison to reactions in typical organic solvents.[6–11] The low aqueous solubility of many reactants can be overcome by the addition of a solubilising agent, such as ethanol or salts; if salts are used, these can have special effects on DA reaction rates.[12–16] Understanding the diverse effects of salts on DA reaction rates will be beneficial for the rational optimisation and control of DA-style reactions in aqueous solution.

Currently, the ways in which aqueous DA reactions can be affected by the addition of salts have been explained in terms of the following three hypotheses:

1. **Water structure and hydrophobic interactions**. Depending on the charge density of ions, salts increase (or decrease) the DA reaction rate,[13] by enhancing (or weakening) the hydrogen bond network of water[17] and consequently strengthening (or weakening) the hydrophobic interaction in the transition state.[6–8,12,13,17]
2. **Internal pressure change**. Salts modify the cohesive energy of water in yet another way, which also affects the reaction rate; this can be quantified through the internal energy of the solution, a long-standing measure of cohesive energy.[12,14,18–21]

3. **Preferential solvation of the DA transition state**. Salts stabilize (or destabilize) the DA transition state through the preferential inclusion (or exclusion) of salts, leading to an enhanced (or reduced) reaction rate.[6,22]

These three hypotheses coexist in the literature and have been used for a long time to explain solvation effects in general.[23,24] The water structure hypothesis (1) has been invoked to rationalize the ion-induced changes in solubility and biomolecular stability alike.[24] The internal pressure hypothesis (2), which has its origins in regular solution theory, has helped explain a wide range of solubility and solvation phenomena mainly in organic solvents. [12,14,18–21,25] The preferential solvation theory (3) comes from the linkage relationship in biomolecular denaturation and stabilization by cosolvents,[26–28] and has also been applied to a wide range of solvation phenomena[29,30] and organic reaction rates. [6,22,31]

The co-existence of three different hypotheses evidences the absence of a fundamental mechanistic understanding of the problem. Indeed, each of the hypotheses suffers from certain limitations as argued below.

1. Persistent ambiguity over the foundation of water structure, especially the absence of a clear answer to the fundamental questions about the real definition of the "water structure" and how this structure changes around ions. The only examinable statement here is that the solute hydration change induced indirectly by ions serves as the dominant factor.[23,24,30,32]
2. Poor correlation between internal pressure and reaction rate, observed upon the incorporation of a wide range of molecular solvents, which is an indication that the correlation for aqueous ionic solutions observed previously may have been limited and fortuitous.[20]
3. Only affinity differences[6,22,31,33] can be determined from preferential solvation, but not affinities between individual species (i.e., water-reactant, salt-reactant, water-TS and salt-TS affinities); whether the DA rate change arises predominantly from the stabilization of the reactants or TS is a question that cannot be answered.

A mechanistic understanding of the problem free from the limitations listed above requires investigation of the following two fundamental aspects:

A. To elucidate the ion-induced change of the reaction rate quantitatively in terms of the water-reactant, salt-reactant, water-TS and salt-TS interactions.
B. To examine whether ion-induced hydration change is the dominant factor responsible for the change of the reaction rate.

As will be shown in the Theory and methods section, the required independent determination of affinities can be achieved via application of statistical thermodynamics, namely, the Fluctuation Solvation-Adsorption Theory (FAST),[23,29] solely from experimental data, by supplementing the salt-induced reaction rate with the volume of reaction, reactant solubility and reactant molar volume. Previously, a combination of the Kirkwood-Buff (i.e., the source of FAST) and TS theories has been used in an attempt to elucidate the organic reaction rates, including DA, but this has produced affinity differences only, [6,22,31] instead of affinities of individual species such as the reactant and TS which are indispensable when looking for a quantitative identification of the dominant cause for the change of reaction rates. What we obtain are the Kirkwood-Buff Integrals (KBIs), parameters which are the difference in pairwise interactions i.e. water-reactant, ion-reactant, water-TS and ion-TS at the molecular level for a reference molecule (the "local" region) relative to the "bulk" region (Figure 1). From this investigation, we can draw a conclusion on the role of solvation on aqueous salt-mediated Diels-Alder reactions based on experimental data, assisted by the transition-state structure as obtained from quantum chemical calculations.

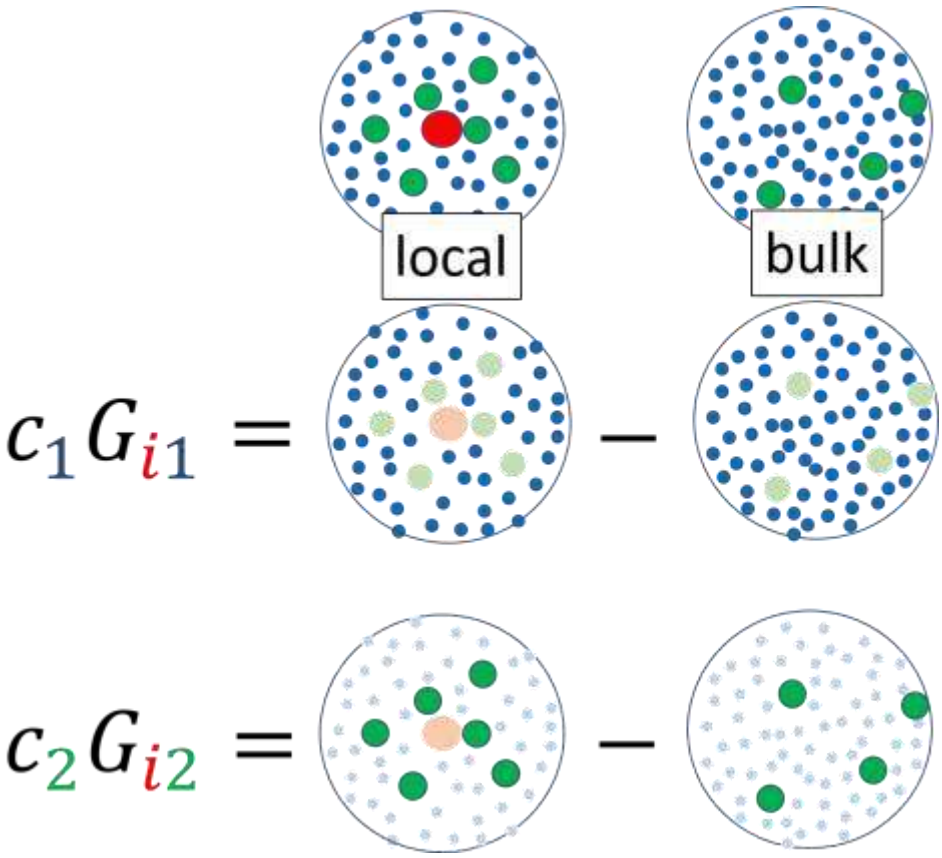
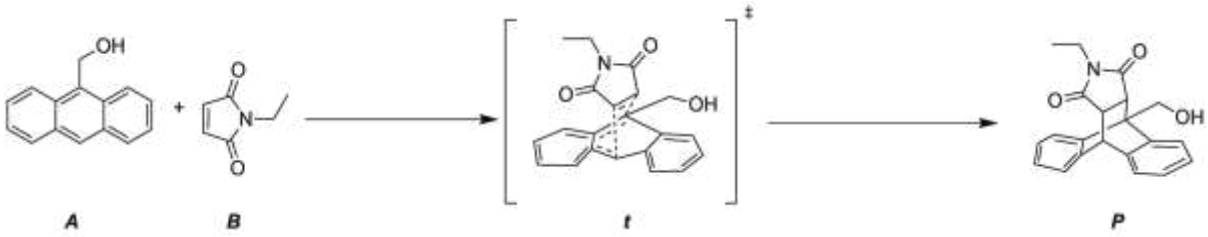


Figure 1: Schematic explanation of the meaning of Kirkwood-Buff integrals (KBI) G_{i1} (between species i and 1) and G_{i2} (between species i and 2) as the difference between "local" (in the vicinity of i) and bulk solutions. c_1 and c_2 represent the molarities of 1 and 2, respectively.

We emphasise here that the major advantage of our approach over the previous ones is the establishment of a direct and explicit link between experimental data (rate of reaction and activation volume) and the quantitative measure of microscopic interactions provided in terms of the Kirkwood-Buff (KB) integrals, as explained in detail in the Theory section. Previous theories, in contrast, cannot provide such a direct link. Ambiguity persisted for decades over how to quantify "water structure" and its change in the presence of salts and how the water structure effect contributes quantitatively to reaction kinetics and equilibria. According to Frank and Franks' classical theory, hydration change induced indirectly by the presence of salts is the cause, yet such effect has been shown to be negligibly small for a number of systems.[32,34] Internal pressure theory refers to the property of the bulk-phase solvent mixture which does not involve any explicit consideration of the presence of the reactant and reactant, thereby unable to provide a quantitative measure of intermolecular interactions involving a reactant and a reactant.

FAST, in contrast, can provide a clear link between the microscopic interactions and the reaction rates observed macroscopically.

As a model reaction, we have chosen the DA reaction between anthracene-9-carbinol (**A**) and N-ethylmaleimide (**B**) (see Scheme 1), which has been studied extensively in aqueous salt solutions.[14,35] All the experimental data needed for theoretical analysis have been published, including the dependence of reaction rates on salt concentration and pressure, as well as the salt-dependent solubility data for the hydrophobic reactant (**A**). The salts we selected include rate-enhancing salts (lithium chloride, LiCl, magnesium chloride, $MgCl_2$ and guanidinium sulfate, $GuSO_4$) and rate-reducing salts (sodium perchlorate, $NaClO_4$, guanidinium chloride, GuCl and guanidinium acetate, GuOAc).



Scheme 1: Structures of anthracene-9-carbinol (**A**) and N-ethylmaleimide (**B**) which undergo a Diels-Alder reaction via the transition state (**t**).

Results and Discussion

The difference in preferential solvation is dominated by salt affinity rather than hydration

The change in preferential solvation between reactants and the transition state, $\Delta G_{u2} - \Delta G_{u1}$, can be calculated via Step I (Eq. (2)) from the reaction rates in the presence of salts.[14] Figure 2 shows that the rate-enhancing salts (LiCl, $MgCl_2$ and $Guan_2SO_4$) exhibit preferential salt solvation ($\Delta G_{u2} - \Delta G_{u1} > 0$), whereas rate-reducing salts ($NaClO_4$, GuCl, GuOAc) show preferential hydration ($\Delta G_{u2} - \Delta G_{u1} < 0$), in line with the previous preferential solvation hypothesis summarised in Introduction.

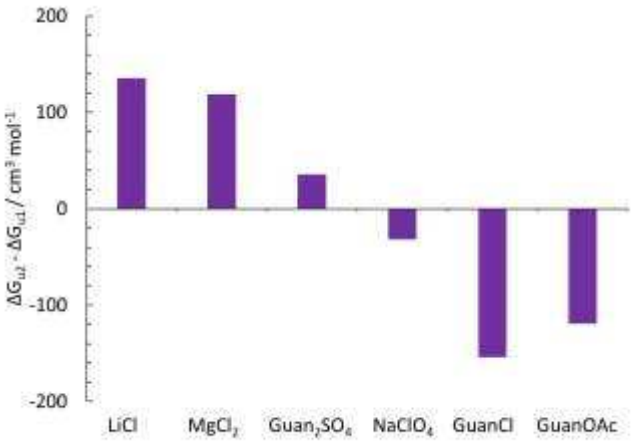


Figure 2: $\Delta G_{u2} - \Delta G_{u1}$ for each of the aqueous salt systems, calculated from literature data.[14]

As preferential solvation, by definition, is the competition between the change of salt ΔG_{u2} and water ΔG_{u1} affinities accompanying $r \rightarrow t$, the true microscopic mechanism of salt-induced rate change can only be understood by an independent determination of the two (Figure 3). This was beyond the scope of the previous preferential solvation hypothesis (see Introduction) and can be achieved only through solving the simultaneous equations (Step II, Eq. (2) and (3)) using the DA activation volume.[35,36]

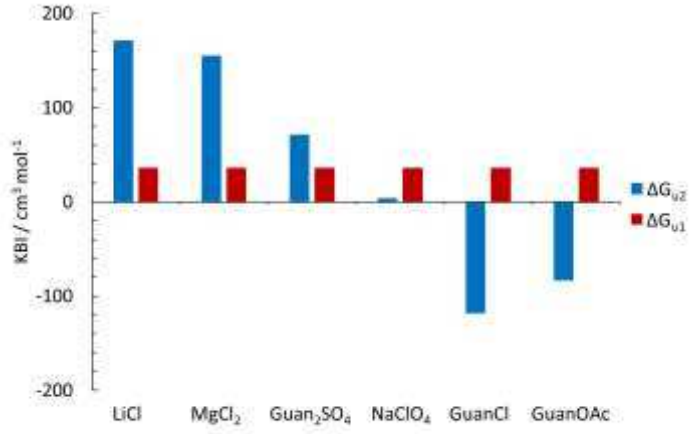


Figure 3: Change in ion interactions (ΔG_{u2}) and water interactions (ΔG_{u1}) for each of the aqueous salt systems studied.

Figure 3 shows that the salt-to-salt variation of the preferential solvation $\Delta G_{u2} - \Delta G_{u1}$ comes exclusively from that of ΔG_{u2}, since ΔG_{u1} is constant when the salt is dilute. In addition, the magnitude of ΔG_{u1} is much smaller than the variation of ΔG_{u2}. Indeed, ΔG_{u1} has a relatively small magnitude in comparison to the majority of ΔG_{u2} values, except for $NaClO_4$, which indicates that it has the smallest effect on the reaction rate. For clarity, we have calculated the solvation shell contributions, $\Delta G_{u1}^{s}$and ΔG_{u2}^{s}, by eliminating via Eq. (6) the excluded volume contribution (Figure 4). ΔG_{u1}^{s} still makes a minor contribution when compared to ΔG_{u2}^{s}.

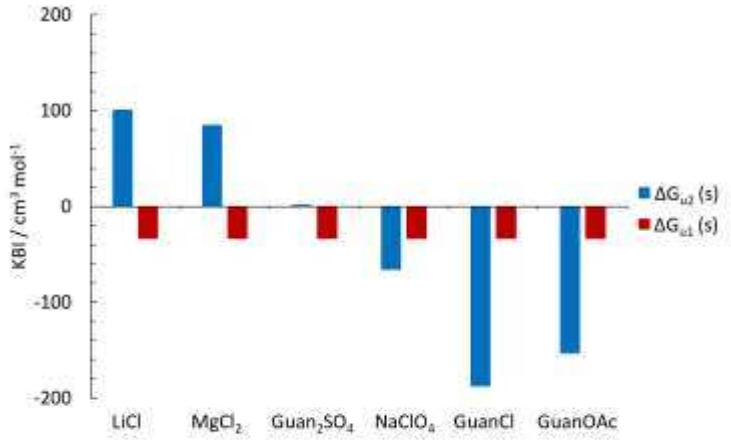


Figure 4: Solvation shell contribution to the change of salt affinity (ΔG_{u2}^{s}) and hydration (ΔG_{u1}^{s}) for each of the aqueous salt systems studied.

The observation that ΔG_{u1}^{s} makes only a minor contribution to preferential solvation change, and consequently to the salt-induced rate change, is in stark contradiction to the water structure hypothesis, according to which the salt-induced hydration change is the dominant driving force. Furthermore, water-water interaction, even if it is modified by the presence of salts, does not make any contribution to the salt-induced change of DA rates (Eq. (2)). We have thus shown that the water structure hypothesis cannot explain the salt-induced change of DA reaction rates.

Salt-reactant vs salt-TS affinities

We established in Section 2.1 that the change in salt affinity accompanying $A + B \rightarrow t$, ΔG_{u2}, makes a dominant contribution to the variation of DA rates. ΔG_{u2}, however, is a difference between salt-reactant ($G_{A2} + G_{B2}$) and salt-TS (G_{t2}) affinities. How does the competition between G_{A2}, G_{B2} and G_{t2} lead to ΔG_{u2}, the driving force for the salt-induced change of DA rate? As shown in Section 2.2, due to the difficulty in extracting interactions between reactant B and salts following from the lack of salt-dependent solubility data in water of B (*N*-ethylmaleimide), the only additional useful piece of information is provided by the values of G_{A2} coming from the solubility data of A (antracene-9-carbinol).

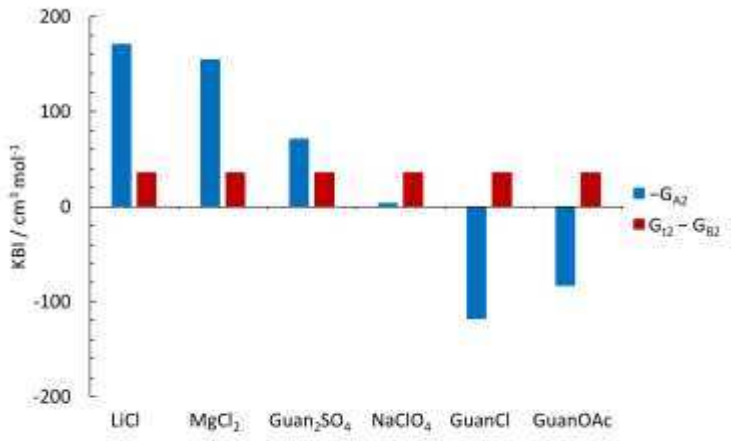


Figure 5: KBI for ion-reactant A interactions, $-G_{A2}$, and combined KBI for ion-reactant B interactions and ion-transition state interactions, $G_{t2} - G_{B2}$.

The rate-enhancing salts (LiCl, $MgCl_2$ and $GuSO_4$), as shown in Figure 5, have a dominant contribution from $-G_{A2}$ to ΔG_{u2}. The more negative G_{A2}, the more unfavourable the interaction between the ***A*** and salts, meaning that the salting out of reactant ***A*** is the major driving force to accelerate the DA reaction. In contrast, the contribution from $-G_{A2}$ is large and negative for the rate-reducing salts (GuCl and GuOAc), making a dominant contribution to ΔG_{u2}. This means that a preferential interaction of these

salts with reactant ***A*** is the driving force behind the rate-reduction seen for these systems, which is consistent with the increased solubility of reactant ***A*** in the presence of these salts.

The generality of our approach

Our theoretical approach, because of its generality, is applicable straightaway to any reactants and cosolvents (electrolytes and non-electrolytes alike) as long as the data on (i) the dependence of reaction rate on cosolvent concentration and (ii) the activation volume are available. Following the FAST formulae already developed,[33,34,37] the effect of cosolvents beyond dilute concentration can be analysed straightway. The only bottleneck is the availability of experimental data, especially the activation volume in the presence of concentrated salts that prevented us from analysing such systems at the present stage.

Conclusion

By combining transition state (TS) theory and fluctuation adsorption-solvation theory (FAST), we have revealed the molecular basis of the salt-mediated aqueous Diels-Alder reaction between anthracene-9-carbinol (**A**) and N-ethylmaleimide (**B**). The advantage of FAST is its ability to quantify individual interactions that contribute competitively to salt-induced rate enhancement. Individual quantification of this type was beyond the reach of the previous approaches and can be achieved only from experimental data. In general, ion interactions with the reactant (**A**) play a dominant role in determining the reaction rate. The current results show that it is the salting out of the reactant A, namely preferential exclusion of the reactant A by ions, as opposed to an increased internal pressure induced by exclusion of ions from the reactants, that drives this salt-mediated aqueous Diels-Alder reaction. The combination of transition state theory and FAST allows for clarification of the mechanism of this salt-mediated aqueous Diels-Alder reaction and provides a methodology that can be applied to a wide range of other salt-mediated aqueous reactions.

Theory and methods

To elucidate how salts affect the rate of Diels-Alder reaction, it is essential to clarify which of the interactions contribute to the reaction rate and to quantify the relevant contributions. To this end, we employ two universal theoretical tools in combination:[38] [41] (1) transition state (TS) theory[39] and (2) fluctuation adsorption solvation theory (FAST),[33,34,40] which originated from the fluctuation solution theory developed by Kirkwood and Buff (KB)[41–44] and encompass solvation and adsorption in mixed solutions.

The statistical thermodynamic treatment in our manuscript assumes established solvent/salt environments of the reactants, TS and product and cannot provide further insights into the dynamics of establishing these solvent/salt environments without performing a molecular dynamics approach, which is outside the scope of the present manuscript. However, as neither solvent nor salts are consumed during the reaction, it can be expected that the solvent/salt environment would retain its composition within the immediate surroundings of the reacting molecules and the extent of ion migration towards or away from the reacting system will be minimal.

Because FAST is a general theory that can be applied universally regardless of the types of cosolvents and chemical reactions, it can reveal the similarity between phenomena from different fields of chemistry. For example, GuCl has long been known as protein denaturant while GuSO4 is a stabilizer,[45] which has been attributed to the accumulation of GuCl around the protein and the exclusion of GuSO4 therefrom.[32,37] We expect that the opposite effect of GuCl and GuSO4 on DA reaction rate can also be attributed to the opposite interaction that the salts are engaged, as recently discussed by Graziano.[46]

Separating preferential solvation into water and salt affinity changes

Consider two reactants, A and B, in aqueous salt solution consisting of water (1) and salt (2), that go through a Diels-Alder reaction, for which the rate-limiting step is $A + B \rightarrow t$ (t: transition state). Let G_{Ai}, G_{Bi} and G_{ti} be the Kirkwood-Buff integrals (KBI) between species i (=1 or 2) and A, B and t, respectively. The change of KBI that accompanies the reaction is defined as

$$\Delta G_{uj} = G_{tj} - G_{Aj} - G_{Bj} \quad (1)$$

ΔG_{uj} can be calculated solely from experimental data, in the following steps:

Step I: TS theory attributes the experimentally-determined reaction rate to the activation free energy $\Delta\mu^{\ddagger}$ (the Gibbs free energy difference between TS and the reactants) at each ion concentration.

Step II: FAST converts the salt concentration dependence of $\Delta\mu^{\ddagger}$ to the water-solute ΔG_{u1} and salt-solute ΔG_{u2} affinity changes that occur as the reaction proceeds, from reactant to transition state ($r \rightarrow t$) as;

$$-\frac{1}{RT}\left(\frac{\partial\Delta\mu^{\ddagger}}{\partial c_2}\right)_{T,P;c_u\rightarrow 0;c_2\rightarrow 0} = \Delta G_{u2} - \Delta G_{u1} \quad (2)$$

where R is the gas constant and T is the temperature. Eq. (2) is an exact result when ion concentration is dilute. Following the standard approach for electrolyte solutions, c_2 refers to ion concentration.[36,47,48]

Step III: Independent determination of the water and salt affinity changes, ΔG_{u1} and ΔG_{u2}, is achieved in FAST by solving elementary simultaneous equations consisting of Eq. (2) and the activation volume, ΔV_u^0, namely, the difference in partial molar volume between TS and reactants,[35] which can be expressed as

$$\Delta V_u^0 = -\Delta G_{u1} \quad (3)$$

Eq. (3), again, is exact for dilute ion concentrations. Note that salt-water interaction, G_{12}, does not make an explicit contribution to the rate of DL reaction. However, it makes an implicit contribution through mediating salt-solute interaction, ΔG_{u2}.[34]

Separating reactant and transition state affinities

Now we separate ΔG_{u1} and ΔG_{u2}, the change of water and salt affinities accompanying $A + B \to t$, into reactant-salt, TS-salt, reactant-water and TS-water affinities. This can be achieved solely from experimental data[29,30,33,47,48] by supplementing Eqs. (2) and (3) with the solubilities and partial molar volumes of the reactants.

To separate the KBI change accompanying reaction (ΔG_{uj}) into components associated with the reactants (G_{Ai} and G_{Bi}) and with the TS (G_{tj}), use can be made of the combination of the following relationships: (i) the dependence of reactant solubility s_r (for $r = A, B$) on (dilute) salt concentration,[29,30]

$$-\left(\frac{\partial \ln s_r}{\partial c_2}\right)_{T,P;c_2\to 0} = G_{r2} - G_{r1} \tag{4}$$

and (ii) the partial molar volume of the reactant, V_r^0 (for $r = A, B$), at the dilute salt limit , [29,30]

$$V_r^0 = -G_{r1} + RT\kappa_T \simeq -G_{r1} \tag{5}$$

Thus, the reactant-water (G_{A1} and G_{B1}) and reactant-salt (G_{A2} and G_{B2}) interactions can be determined from Eqs. (4) and (5). When these are combined with the interaction changes determined earlier (ΔG_{u1} and ΔG_{u2}), the TS-water (G_{t1}) and TS-salt (G_{t2}) interactions can also be quantified, thereby providing complete quantification of how salt and water interact with the reactant and TS.

However, it is difficult to quantify the affinity of a high-solubility reactant (***B***) to water and salt, because reactant-reactant affinity becomes inseparable due to its high solubility in water. In contrast, the affinity of a low-solubility reactant (***A***) to water and salt can easily be determined using Eqs. (4) and (5). In this case, ΔG_{ui} can be decomposed into $-G_{Ai}$ (contribution due to the affinity between A and i) and additional contributions ($G_{ti} - G_{Bi}$).

Solvation shell contributions to KBI

A KBI, G_{ij}, not only contains information on the distribution of the species j around i but also a large negative contribution due to the excluded volume, arising from the impenetrability of j to the core of i. Once the excluded volume, V_{ij} is evaluated from the experimentally or quantum chemically obtained molecular structure,[33,49] we can obtain the solvation-shell contributions to KBIs in the following manner:

$$G_{ij}^{s} = G_{ij} + V_{ij} \tag{6}$$

To calculate the excluded volumes, the gas-phase geometries of anthracene-9-carbinol, N-ethylmaleimide and the Diels-Ader transition state were optimized using density functional theory (DFT), at the B3LYP-D3(BJ)/def2-SVP level (B3LYP with Grimme's D3 empirical dispersion corrections and Becke-Johnson damping, within the standard def2-SVP basis set). Each optimized geometry was confirmed as a local minimum through diagonalization of the respective analytic nuclear Hessian. All of these calculations were carried out using GAUSSIAN16.[50] As anthracene-9-carbinol allows two conformers, differing in the orientation of the hydroxyl group, and the Diels-Alder transition state allows four conformers, differing in the orientations of the hydroxyl and ethyl groups, the geometries of all (two or four, respectively) conformers were optimized and those of lowest energies were selected for the excluded volume calculations. For each species, the excluded volume was calculated as the volume within the Connolly surface[51] for a probe radius of 1.4 Å, using Connolly's Molecular Surface Package version 3.9.2.

Extension to higher salt concentrations

Our theoretical approach can straightforwardly be generalized to higher salt concentrations. To do so, Eq. (2) can be generalized into the following form:

$$-\frac{1}{RT}\left(\frac{\partial\Delta\mu^{\ddagger}}{\partial\mu_2}\right)_{T,P;c_u\to 0} = \frac{\Delta G_{u2}-\Delta G_{u1}}{1+c_2(G_{22}-G_{21})} \quad (7)$$

The additional KBIs appeared here, G_{22} and G_{21}, can be calculated from the activity and density data.[47,52] Note that the water-water interaction, G_{11}, does not appear in this rigorous theory, showing that the water-water interaction change in the presence of the salt is not an explicit factor influencing kinetics. Note also that water-water interaction, G_{11}, does not appear in Eq. (2) as well. As we have shown previously, the sign of $-\frac{1}{RT}\left(\frac{\partial\Delta\mu^{\ddagger}}{\partial\mu_2}\right)_{T,P;c_u\to 0}$ is determined by the competition between ΔG_{u2} and ΔG_{u1} is a dominant factor in determining the cosolvent's role on reaction equilibria and kinetics – in the present case the acceleration or retardation of a chemical reaction.[34,52] In contrast, the contribution from the bulk solution structure $1+c_2(G_{22}-G_{21})$ only plays the secondary role in modulating the effect coming from the competition between ΔG_{u2} and ΔG_{u1}.[52] Thus the solvent plays an implicit role in mediating the solute-cosolvent interaction.

The present theory we will be applicable to any principle solvents and any cosolvents as long as the relevant experimental data are available.

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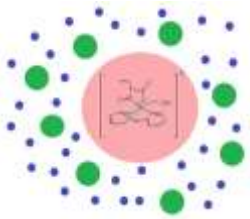
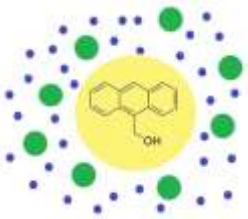
ToC graphics



Preferential salt-TS interaction

Rate of reaction increased



Preferential salt-reagent interaction

Rate of reaction reduced